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**Title: Developments in structural and functional neuroimaging in infants with critical congenital heart disease at risk for neurodisability**

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## **Abstract**

### *Purpose of review:*

This review aims to integrate data on brain dysmaturation and acquired brain injury in fetuses and neonates with congenital heart disease, including the contribution of cardiovascular physiology, the relation to functional outcome and future preventive and regenerative strategies.

*Summary:* The antenatal and neonatal period is critical for brain development, and the brain is particularly vulnerable to hemodynamic disturbances during this time. As such, brain dysmaturation and acquired brain injury have consequences for long-term neurodevelopment. In critical congenital heart disease, brain dysmaturation and injury coexist. Altered cerebral perfusion and decreased cerebral oxygen delivery in the antenatal period have impact on brain development, and postnatal hemodynamic fluctuations cause additional brain injury. In compromised fetuses and neonates, MR imaging is an important and valuable tool to detect altered brain development and acquired brain injury. MRI findings can be used to evaluate potential clinical risk factors for brain dysmaturation and injury, and are also of value in the prediction of neurodevelopmental outcome at an early stage. Information on timing of brain dysmaturation and acquired brain injury can be used to develop neuroprotective and regenerative strategies.

### Running title:

Neuroimaging in congenital heart disease

### What this paper adds

- What is the value of functional and structural neuroimaging in detecting brain dysmaturation and acquired brain injury in fetuses and neonates with congenital heart disease, and what are the future therapeutic and prognostic perspectives?
- How does cardiovascular physiology contribute to the differences in brain maturation and acquired brain injury?
- Can the range of functional outcomes seen in children with congenital heart disease be explained by brain dysmaturation and acquired brain injury in the fetal and neonatal period?
- 

### Key messages for clinical practice

Neuroimaging is important in fetuses and neonates at risk of neurodisability due to brain developmental disturbances and injury. Using different MR sequences structural and functional brain development in addition to aberrant development and acquired brain injury can be detected.

## **Abbreviations**

ADC	Apparent diffusion coefficient
ASL	Arterial spin labeling
CGM	Cortical gray matter
CHD	Congenital heart disease
CoA	Coarctation of the aorta
dMRI	Diffusion MRI
FA	Fractional anisotropy
HLHS	Hypoplastic left heart syndrome
MRI	Magnetic resonance imaging
NAA	N-acetyl aspartate
SVP	Single ventricle pathology (all forms of univentricular CHD)
TGA	Transposition of the great arteries
WM	White matter
WMI	White matter injury

## **Introduction**

With the increasing survival of young infants with congenital heart disease (CHD) the focus shifts towards the long-term future of these patients, unfortunately revealing a high risk of impaired neurodevelopment (1). Although literature on this topic is contradictory, most recent studies with comparison to healthy controls confirm the reverse outcome in this group. As surgical techniques and intensive care improve, more of the high-risk patients will nowadays survive. At the age of 14 months, psychomotor- and cognitive development indices are lower than normative means in patients with single ventricle pathology (2, 3). At school age, lower intelligence quotients than in the average population are measured in CHD survivors (4). In adolescence, CHD patients still show lower intelligence quotients than their healthy peers (5) accompanied with poorer perceptual reasoning and working memory (5, 6). Unfortunately, psychiatric disorders as autism and hyperactivity disorder have been noticed in higher incidences in adolescents born with critical CHD (7, 8). This warrants further investigation to optimize therapeutic and preventive strategies and improve neurological outcome in this patient population.

Important phases of brain development take place in the last part of gestation and early postnatal life, at both (micro)structural and functional level. This includes increase in brain size, cortical folding, neuronal migration, synaptogenesis, the onset of myelination and cortical activity. The developing brain is particularly vulnerable to hemodynamic disturbances, hypoxia and inflammation. In CHD the fetal circulation has anatomically changed, disturbing optimal brain blood content and brain perfusion (9). Persistently decreased oxygen delivery to the brain causes metabolic, structural and functional adaptations in the fetal brain. Postnatally, when the brain is still under development, neonates with critical CHD are exposed to several high-risk events with the potential to cause acquired brain injury. These events can cause fluctuations in cerebral perfusion which is related to subsequent brain damage. With different sequences, MRI has the ability to provide insight into brain development and acquired brain injury in compromised fetuses and neonates. In figure 1 an overview is presented with the most useful timing and indications of different MRI sequences.

This review aims to integrate data on brain dysmaturation and acquired brain injury in fetuses and neonates with congenital heart disease, including the contribution of cardiovascular physiology, the relation to functional outcome and future preventive and regenerative strategies.

## **Fetal and neonatal cardiovascular physiology and brain blood supply**

The fetal circulatory system has the optimal design to deliver highly oxygenated blood from the placenta to the brain. In the normal fetal circulation, around 25% of the ventricular output will flow to the brain and the brain takes 50% of the total fetal oxygen consumption (10). An anatomical change in fetal circulation will have consequences for brain blood content and brain perfusion. Congenital heart malformations develop from the 6-7<sup>th</sup> week of gestation onwards and alterations in cardiac output are already noticed in the second trimester of pregnancy. In utero, a

right-to-left shunt is normally present, securing oxygenated and nutrient-rich placental blood to flow to the left ventricle, and out the aortic valve to the brain and other organs. Two shunts are known; the foramen ovale between the two atria and the ductus Botalli (i.e. ductus arteriosus) between pulmonary artery and aorta.

In many of the critical cardiac defects, the anatomical change will lead to disturbances in this right-to-left shunt causing mixed or low blood content delivery to the brain. In the situation of left outflow tract obstruction (Hypoplastic left heart syndrome (HLHS), aortic valve stenosis) the internal carotid arteries are supplied via retrograde flow from the ductus Botalli (normally antegrade flow from the left ventricle) with mixed blood content. A change in right-to-left shunt is also seen in other types of single ventricle pathology (SVP) with hypoplastic right of left ventricle. In transposition of the great arteries (TGA), the aorta is connected to the right ventricle causing a left-to-right shunt, resulting in mixed blood content delivery to the brain (11). Brain perfusion can also be altered as now the right ventricle has to provide the systemic circulation. In other critical cardiac defects (such as right outflow tract obstruction (including hypoplastic right heart and pulmonary atresia), coarctation of the aorta (CoA), septal defects and truncus arteriosus) the anatomical change does not disturb the fetal right-to-left shunt. In many cases the brain can receive oxygen- and nutrient-rich blood, but perfusion of the brain can still be suboptimal.

In late gestation, 10% reduction in oxygen saturation of blood supplied to the brain (measured in the major systemic vessels) was described in a group of fetuses (N=30) with either left- or right outflow tract obstruction (12). This led to a 15% reduction in cerebral oxygen delivery and 32% reduction in oxygen consumption for fetuses with CHD compared to their healthy peers (N=30). No differences in fetal cerebral blood flow or oxygen extraction were seen.

The neonatal circulation is different from the fetal circulation, as the pulmonary circulation is bypassed in the fetal phase. Therefore with the transition from fetal to neonatal life, the type and amount of disturbance in circulation by a specific cardiac defect will change. Decrease in pulmonary resistance causes an increase in pulmonary flow. In a recent postnatal MRI study (13), performed before surgery, cerebral blood flow was comparable between neonates with SVP, TGA, coarctation of the aorta (N=32) and healthy controls (N=31). But SVP and TGA had both reduced oxygen delivery compared to coarctation of the aorta and healthy controls. As blood flow was comparable, this is mainly explained by the decreased arterial oxygen saturation: 98% in healthy controls, 98% in coarctation, 84% in SVP, 86% in TGA.

The previous mentioned critical congenital heart defects require cardiac repair in the first weeks of life using cardiopulmonary bypass. The transition from in utero to ex utero life (with decrease in pulmonary resistance), perioperative problems (such as apneas, hypotension, heart rhythm disorders) and major cardiopulmonary bypass surgery are associated with alterations and fluctuations in cerebral perfusion and oxygenation, where neonates are known to have less auto regulatory capability and anti-oxidant scavenging capacity to cope with such problems.

## Structural brain development under changed cardiovascular physiology

Infants with critical CHD (requiring neonatal cardiac surgery with cardiopulmonary bypass) have smaller head circumferences at birth than healthy controls (17), and lower z-scores in fetal head circumference and bi-parietal diameter are already seen from the second trimester onwards (18). With the ability to obtain volumes of specific brain structures, MRI studies reveal which brain tissues are responsible for smaller head circumferences.

**Table 1** provides an overview of fetal and neonatal brain volume studies in mixed cohorts of critical CHD. All studies show significant reductions in volume of the total brain, white matter (WM) and cortical gray matter (CGM) in CHD fetuses *and* CHD neonates when compared to controls (12, 13, 19, 20). In antenatal studies, with increasing gestation higher deviation of total brain volume in CHD is seen (21-23). An imaging example of different brain volumes obtained with MRI is provided in **figure 2**.

In the fetal phase, reduced flow through the systemic ventricle (measured with echocardiography) is associated with smaller total volume of the brain (23). This is most pronounced in HLHS and TGA, as lower brain volume was also associated with lower combined ventricular cardiac output, or absence of antegrade flow through the aortic valve. Also, reduction in oxygen delivery and oxygen consumption is associated with decreased total brain volume (12), which is most severe in HLHS when compared to biventricular pathology.

CGM and WM show reductions in volume of at least 10% in HLHS from the 30<sup>th</sup> week onwards (24) but also in tetralogy of fallot (21). No CHD category analyses have been done regarding CGM and WM in prenatal studies. In neonatal studies, WM and CGM are comparably reduced in TGA and SVP (20, 25). As both structures occupy one third of the intracranial space, these explain the majority of reduced total brain volume. The cerebral cortex is one of the structures with relatively the highest volumetric increase in the last part of gestation and might therefore be relatively more affected than other brain structures (26).

Structural maturation of the cortex is expressed in degree of cortical folding (i.e. gyrification). The fetal brain is still smooth around 24 weeks, and cortical folding occurs rapidly in the last part of gestation, with at term the cortex being reorganized into a pattern close to that of the adult brain (27). Fetal and neonatal cortical folding is delayed in fetuses and neonates with SVP compared to healthy controls (24, 25, 28), as is shown in **table 1**. An example of cortical folding measurement using MRI is provided in **figure 2**. Less complex sulci (delayed first appearance or reduced depth) can already be seen in HLHS fetuses around 30 weeks of gestation (24). Neonates with TGA (N=21) show comparable degree of cortical folding as healthy controls (25). In both SVP and TGA, mixed blood content delivery is supplied to the brain. But in HLHS, the aortic arch (supplying the internal carotid arteries) has retrograde perfusion via the ductus Botalli. Apparently, the latter is playing a larger role in the delay in cortical folding. Postoperative cortical folding (2 weeks after surgery, N=31)

is negatively influenced by lower birth weight and preoperative balloon atrioseptostomy (25). In addition, the basal ganglia and thalami are also known to be smaller in SVP and TGA when compared to healthy controls, in both fetal (24) and neonatal (20) period. The cerebellum is an important structure undergoing rapid (three fold) increase from the 30<sup>th</sup> week of gestation onwards (26), and is at this age of comparable volume in fetuses with and without CHD (21, 22). In the postnatal period (before surgery), a reduction of 20% in cerebellar volume in SVP and TGA neonates (N=19) has been observed (20).

Smaller postnatal brain volumes are associated with abnormal neurobehavior in CHD newborns before their open-heart surgery (30). Although data on the association between fetal and neonatal brain volumes and long-term neurodevelopmental outcome in critical CHD is lacking, the importance of optimal brain growth has been shown. At 1 year of age, WM volume is predictive of language development at the same time point in TGA infants. In adolescents with cyanotic congenital heart disease, total brain volumes are significantly smaller than in healthy controls, and this decrease is strongly correlated with total IQ, verbal comprehension, perceptual reasoning and working memory (31). Delays in these cognitive functions are also associated with lower hippocampal volume in CHD adolescents (a structure that cannot be measured in fetuses and neonates) (32). Studies in preterm infants have highlighted the importance of optimal structural volumetric brain growth (33), with especially larger WM and cerebellum being related to better cognition and processing speed at (pre-)school age. Impairments in cortical folding at term age are known to be associated with subsequent alterations in cognitive outcome in preterm neonates (34-37).



## Microstructural white matter maturation: cardiac risk factors and functional outcomes

Many of the maturational processes that take place in the last part of gestation and early postnatal life are at microstructural level, for example white matter axonal growth and myelination. Improved microstructural development of the white matter is associated with higher cognitive functioning, visual-spatial skills and memory in adolescents with TGA (8). Also, early life perioperative factors such as gestational age, shorter duration of intraoperative cooling, longer intensive care stay after cardiac repair and greater number of total operations are predictors of reduced white matter microstructure as adolescent (41).

Contrast in diffusion MRI (dMRI) is based on the motion of water molecules (42). The diffusion profile of water molecules can vary across the brain due to the high complexity of the different biological structures. In the cerebrospinal fluid, water molecules are allowed to move relatively freely. Diffusion is described here as being *isotropic*, as the average displacement of water molecules is equal in all directions. In the white- and gray matter, water movement is restricted in certain directions by the presence of cellular architecture (i.e. axonal density and myelination), causing diffusion to be *anisotropic*. The influence of cerebral tissue on water movement enables dMRI to be highly sensitive to microstructural changes, including those changes associated with brain development and brain injury. Higher fractional anisotropy (FA) in the white matter means increased cellular architecture, i.e. increased microstructural development. An example image of diffusion tensor imaging, a diffusion sequence with the ability to map the direction of diffusion, is provided in **figure 2**.

The first study using dMRI to examine disrupted postnatal brain development in neonates with CHD observed that FA values were lower throughout the brain prior to surgery in both SVP and TGA when compared to healthy controls (43). These dMRI measures presumably reflect abnormal in utero microstructural brain development. Other studies have replicated these findings using a variety of dMRI analysis approaches (44-46). Also, postnatal white matter FA is lower in CHD neonates with brain injury compared to CHD neonates without brain injury (44). This shows dysmaturation of the brain to be accompanied with an increased risk of acquiring brain injury in early life. The corpus callosum is an important white matter structure with decreased FA in neonates with TGA (45), which is associated with impaired cognitive functioning at pre-school age in preterms (48).

Altered WM microstructure prior to surgery appears to be influenced by smaller aortic diameter in the presence of aortic atresia in SVP (49). In contrast, brain microstructure is less disrupted in those cases with a prenatal diagnosis, which may be due to earlier use of prostaglandin E1 (to maintain the ductus Botalli) (50). The functional impact of early microstructural abnormalities identified on dMRI in CHD infants has been highlighted recently in a study showing that altered FA values are associated with altered functional connectivity using electroencephalography prior to surgery (51). This shows the relation between structural and functional brain development.

## Structural and functional brain networks in congenital heart disease

*Structural* connections between different brain regions can be estimated using dMRI based tractography, and together be placed in the context of a network, or graph. Graph theory provides a mathematical framework for the analysis of structural brain networks. Most commonly, important nodes are defined on the basis of degree (i.e. the number of connections to other nodes) or centrality (i.e. the probability that pathways between other nodes pass at least once through the node of interest) (52). Graph-theoretical, structural connectivity analyses have demonstrated that network connectivity is present at term age. In preterm infants, the presence of well-connected cortical hubs are already evident at 30 weeks gestation (53). These hubs display a high degree of connectivity and, even at this early age, form a densely connected subnetwork, forming a putative “rich club” of connections. These clubs are centered in the heteromodal association cortex, in the superior frontal and parietal lobes, and include nodes in the basal ganglia and hippocampi.

*Functional* networks can be examined using functional resting state MRI. We know from work in the developing preterm brain that functional networks are present in newborns and closely resemble those reported in adults (54, 55). Evidence suggests functional development to proceed according to well-established hierarchy. Although the presence of executive networks, including the default mode and fronto-parietal attentional networks, at such a young age also suggests that foundational network activity is established in advance of the cognitive functions that they are thought to underlie.

To date, there have been no reported structural or functional network based studies on the neonatal brain in CHD. However, in adolescents, who had undergone repair of d-TGA in infancy, disrupted network organization (alterations in network connectivity, integration and segregation) was associated with worse ADHD outcomes (56) and cognitive dysfunction (57). Further research on structural networks is warranted. Functional MRI networks have been explored in CHD adolescents and adults (58, 59). In a recent study, adolescents who underwent surgery for CHD (n=17) displayed altered fMRI activity during a working memory test compared to controls (59). CHD subjects exhibited less task-induced deactivation within left precuneus- and right inferior frontal cortical area during the task. Importantly, prefrontal fMRI deactivation correlated with improved working-memory performance in the CHD group. Future studies with larger sample sizes are required to determine the relationship between fMRI findings and executive performance in survivors of CHD.

## Range of acquired neonatal brain injury and contribution to functional outcome

As shown in **figure 1**, different types of neonatal acquired brain lesions are seen in critical CHD. Acquired neonatal brain injury is in most cases clinically silent (especially when sedation is given (61)) highlighting the importance of neuroimaging in this group. When of ischemic origin, which is most often the case in CHD, these lesions can be seen on dMRI (as shown in **figure 2**). Brain tissue edema as a reaction to ischemia will lead to restriction of water molecular diffusion which is displayed as high intensity on dMRI and with reduced apparent diffusion coefficient (ADC) values. Subsequently, pseudo normalization of the ADC will occur and dMRI should, therefore, be performed within 3-7 days after injury (62). **Table 2** compares the incidences of brain injury in SVP and TGA patients.

White matter injury (WMI) is described in full-term neonates with CHD in remarkably high incidences (43). WM lesions are characterized as hypo- and hyper-intense on T2- and T1 weighted imaging respectively, and scoring systems differ between research groups (63). In CHD, WM lesions can often be found in the watershed areas (areas perfused by the most distal branches of two main cerebral arteries) which are usually due to (acute) hypo perfusion. In neonates, auto regulatory mechanisms are still vulnerable as they lack the full ability to cope with fluctuations in cerebral perfusion. In neonates with critical CHD, lower preoperative oxygen saturation and preoperative hypotension are associated with increased risk of *preoperative* WMI (64-67), as is postnatal diagnosis of the heart defect (50). *Postoperative* WMI is associated with lower hematocrit and arterial carbondioxide during surgery, as also post-operative complications and lower mean blood-pressures (64, 68, 69). Patients with SVP show longer length of post-operative stay, more additional operations, more often cardiopulmonary resuscitation and extracorporeal membrane oxygenation than patients with TGA (70), but incidences of acquired brain injury are similar between the two groups (see table 2).

Arterial ischemic stroke is thought to have a thromboembolic origin. Cortical and deep gray matter focal strokes are common in the CHD population, as is shown in table 2. Main branch strokes always include WM, CGM and basal ganglia. After cardiopulmonary bypass surgery in CHD newborns, focal infarctions of the basal ganglia and CGM are often seen (**table 2**). Branches of the middle cerebral artery seem to be most often involved, followed by the posterior- and anterior cerebral artery (68). Balloon atrioseptostomy is associated with preoperative stroke in most studies (64, 66, 71, 72) with the main underlying etiology thought to be embolic, but disturbances in cerebral perfusion cannot be excluded.

WM lesions are also characteristic of preterm neonates, which might reflect the shared WM vulnerability (and immaturity) between preterm and CHD neonates. Preoperative brain injury was found to be accompanied by decreased microstructural WM maturation in several studies (44, 46, 64). In preterm infants WMI is thought to have an inflammatory origin, but in critical CHD neonates no relationship between WMI and inflammatory responses have been observed to date (74, 75). Lower postnatal cerebral blood flow (using ASL) is associated with higher incidences of preoperative WM abnormalities in CHD neonates with SVP and TGA (16). This

suggests a link between abnormal cerebral hemodynamics, brain immaturity and acquired brain injury in critical CHD.

Risk factors as lower birth weight, genetic syndrome, longer mechanical ventilation after surgery and postoperative complications are risk factors of delayed psychomotor and mental outcome at the age of 14 months. Data on 1770 children (ICCON database) revealed longer total support time, extracorporeal membrane oxygenation, ventricular assist device support and longer post-operative ICU stay to be associated with lower mental and psychomotor scores at the age of 13 months (70). But also lower birth weight and genetic syndrome are important risk factors for preschool outcome in children with CHD (2).

The prognosis of acquired brain injury mainly depends on location and extent. Involvement of the posterior limb of the internal capsule and cerebral peduncles on diffusion MRI is predictive of (unilateral) spastic cerebral palsy, which can already be present from 3 months of age onwards (76). Acquired stroke and WMI show a trend of relation to lower psychomotor outcome at the age of 2 years (74). The development of epilepsy after the neonatal period is reported in various incidences, but normally responds well to drug-therapy (77). On the prognosis of cognitive outcome, there is less consensus regarding acquired brain injury. This may partly be due to the relatively short period of follow-up to date after neonatal surgery for congenital heart disease. Lower cognitive scores at the age of 12 months are seen in infants who had preoperative acquired brain injury (78).

## **Future perspectives**

This review has shown substantial gaps in current knowledge on the relation between early life brain dysmaturation and acquired brain injury with functional outcomes on the long-term. Neuroimaging is important in fetuses and neonates with congenital heart disease, to reveal the presence of brain dysmaturation and acquired brain injury and provide opportunities for early intervention. Close monitoring of the infant, child, adolescent and adult with CHD is necessary, as neurodevelopmental impairments are common and require additional support. Preschool survivors with SVP show similar neurodevelopmental outcomes as children with TGA and other types of biventricular physiology (80, 81). This shows the importance of neurodevelopmental follow-up in all patients who require cardiac surgery with cardiopulmonary bypass in the first weeks of life. Early life neuroimaging and life-long follow-up should be combined to reveal the effect of brain alterations in the most critical period of brain development to subsequent neurological outcome. The interaction between (epi)genetics, cardiovascular physiology and neurological development requires further elucidation in the prediction of these patients with the highest risk.

With the identification of the most critical time points of onset of brain dysmaturation and acquired brain injury, neuroimaging is fundamental in the development of neuroprotective strategies. In other high-risk neonatal populations with hypoxic-ischemic injury or neonatal stroke, clinical trials are exploring the protective and regenerative role of several drugs as allopurinol, EPO, xenon gas and melatonin. These drugs might have a beneficial role in the pathways set in motion after fetal or neonatal hypoxia and the following reoxygenation and reperfusion (82). Currently, allopurinol and EPO are both very attractive candidates. Allopurinol has the ability to scavenge free radicals (released after the hypoxic incident), where EPO has an anti-inflammatory role. Experimental therapies with for example stem cells might also be promising in our near future. Fetuses and neonates with critical CHD are experiencing both chronic hypoxia as acute hypoxic-ischemic incidents, and might benefit from these promising neuroprotective interventions.

## **Conclusions**

This review highlights the value of early life structural and functional neuroimaging and lifelong follow-up in compromised fetuses and neonates with critical congenital heart disease. As major developmental phases take place in the antenatal and neonatal period, a time when the brain is particularly vulnerable to hemodynamic disturbances, brain dysmaturation and acquired brain injury have consequences for long-term cognition, motor outcome, behavior and executive functioning. In critical congenital heart disease, brain dysmaturation and brain injury coexist. Altered cerebral perfusion and decreased cerebral oxygen delivery in the antenatal period have impact on brain development, and postnatal hemodynamic fluctuations cause additional brain injury. Different MR sequences allow examination of functional and structural brain development and have the ability to characterize aberrant brain development and acquired brain injury. These findings can be helpful in the design of therapeutic and preventive strategies aimed at optimizing neurodevelopmental outcome.

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## Tables

<b>Fetal volumes</b>	<b>Inclusion</b>	<b>Cases <i>n</i></b>	<b>Controls <i>n</i></b>	
Masoller, 2016 <sup>15</sup>	complex & simple CHD	58	58	<b>Reduced TBV.</b>
Schellen, 2015 <sup>18</sup>	ToF	24	24	<b>Reduced TBV, CGMV, WMV. Comparable CBV.</b>
Sun, 2015 <sup>12</sup>	complex CHD	30	30	<b>Reduced TBV</b>
Andescavage, 2015 <sup>19</sup>	complex & simple CHD	41	94	<b>Comparable CBV.</b>
Clouchoux, 2013 <sup>21</sup>	HLHS	18	30	<b>Reduced CGMV, WMV and BGV. Reduced GI and CS.</b>
Limperopoulos, 2010 <sup>20</sup>	complex CHD	50	55	<b>Reduced TBV</b>
<b>Postnatal volumes</b>				
Lim, 2016 <sup>13</sup>	complex CHD	32	31	<b>Reduced TBV</b>
Rhein, 2015 <sup>17</sup>	complex CHD	19	19	<b>Reduced TBV, CGMV, WMV, BGV and CBV</b>
Ortinou, 2013 <sup>25</sup>	complex CHD	15	12	<b>Reduced GI and CS</b>
<b>Postoperative volumes</b>				
Claessens, 2016 <sup>22</sup>	complex CHD	23	18	<b>Reduced CGMV and WMV. Reduced GI and CS.</b>

**Table 1:** Overview of current literature on brain volume studies in fetuses and neonates with CHD. The studies were included when brain volumes or cortical folding was examined using MRI, and patients were compared to healthy controls. When multiple studies from one center showed similar results on the same population, only one of those studies was included. *CHD: congenital heart disease. HLHS: hypoplastic left heart syndrome. ToF: tetralogy of fallot. TBV: total brain volume (only brain structures, excluding cerebrospinal fluid). CGMV: cortical gray matter volume. WMV: white matter volume. BGV: basal ganglia volume. CBV: cerebellar volume. GI: gyrification index. CS: cortical surface.*

Preoperative injury Studies	SVP <i>n</i>	TGA <i>n</i>	Any injury		WMI		Infarction	
			SVP	TGA	SVP	TGA	SVP	TGA
Peyvandi, 2016 <sup>42</sup>	57	96	35%	39%	28%	29%	12%	25%
Brossard-Racine, 2016	20	31	45%	29%				
Desai, 2015 <sup>65</sup>	13	6			31%	17%		
Bertholdt, 2014 <sup>56</sup>	8	22			0%	32%		
Mulkey, 2013 <sup>37</sup>	18	14	50%	50%				
Dimitropoulos, 2013 <sup>55</sup>	22	71			32%	21%	17%	24%
Beca, 2009 <sup>63</sup>	13	44			23%	27%	8%	5%
Postoperative new injury Studies					new WMI		new Infarction	
					SVP	TGA	SVP	TGA
Desai, 2015 <sup>65</sup>	16	14			75%	29%		
Bertholdt, 2014 <sup>56</sup>	8	22			13%	5%		
Dimitropoulos, 2013 <sup>55</sup>	29	65			14%	19%	14%	8%

**Table 2:** Overview of current literature on brain injury in fetuses and neonates with critical CHD. Brain injury studies showing numbers for SVP and TGA patients separately were included. When multiple studies from one center showed similar results on the same population, only one of those studies was included. *CHD: congenital heart disease. SVP: single ventricle pathology. TGA: transposition of the great arteries. WMI: white matter injury.*

## **Figure legends**

**Figure 1:** In this figure an overview of normal microstructural (dark purple) and structural (light purple) brain developmental phases from the 20<sup>th</sup> week of gestation until the neonatal period are shown. In the second part cerebral changes (dark blue) and brain injuries (light blue) in fetal and neonatal populations at risk for neurodisability are presented. Below each developmental phase or alteration the most convenient neuroimaging or neuromonitoring techniques to display the concerning part are shown. \*No MRI modality, outside the scope of this review.

**Figure 2:** This figure shows different MR images and post-processing images of neonates with critical CHD. A and B show T2-weighted imaging based brain volumes at different axial levels (pink=CGM, blue=unmyelinated WM, purple=brainstem, red=cerebellum, light red=cerebral spinal fluid, turquoise=ventricles, green=basal ganglia, yellow=myelinated WM). C shows a 3D reconstruction of the inner CGM surface with the mean curvature of this surface (yellow=zero curvature, blue=negative curvature, red=positive curvature). Figure A-C are the result of an in-house developed method used in our CHD population (83). D and E are results of axial DWI displaying the high intensity of respectively periventricular white matter lesions and bilateral focal infarctions of the basal ganglia and thalamus in two CHD patients. In F an example of diffusion tensor imaging in a neonate with critical CHD can be found at the axial level of the posterior limb of the internal capsule (blue superior-inferior tracts) and corpus callosum (red left-right tracts).